PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
RIDOUT & MAYBEE LLP
2400 - One Queen Street East
TORONTO, Ontario
Canada, M5C 3B1

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	03 May 2005 (03-05-2005)
Applicant's or agent's file reference 42121-0016	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/002119	13 December 2004 (13-12-2004)	12 December 2003 (12-12-2003)

International Patent Classification (IPC) or both national classification and IPC
IPC7 A61K 38/48, G01N 33/92, C12Q 1/02, A61K 38/17, A61K 45/00, A61P 3/06

Applicant
THE UNIVERSITY OF MANITOBA ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[X]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer

André Pilon (819) 997-2996

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] This opinion has been established on the basis of a translation from the original language into the following language ,which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

   a. type of material

      [ ] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [ ] in written format

      [ ] in computer readable form

   c. time of filing/furnishing

      [ ] contained in the international application as filed.

      [ ] filed together with the international application in computer readable form.

      [ ] furnished subsequently to this Authority for the purposes of search.

3. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[ ] claim Nos.

because:

[X] the said international application, or the said claim Nos. 1, 2, 5, 6 and 30
relate to the following subject matter which does not require an international preliminary examination *(specify)* :

Remark: Although claims 1, 2, 5, 6 and 30 are directed to a method of medical treatment of the human or animal body, which the Authority is not required to search under Rule 39.1(iv) of the PCT, the search has been carried out based on the alleged effects of the compositions.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claim Nos.
are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed.

[ ] no international search report has been established for said claims Nos.

[ ] the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form [ ] has not been furnished

[ ] does not comply with the standard

the computer readable form [ ] has not been furnished

[ ] does not comply with the standard

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. IV Lack of unity of invention

1. [ ] In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has :

   [ ] paid additional fees

   [ ] paid additional fees under protest

   [ ] not paid additional fees

2. [ ] This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   [X] complied with

   [ ] not complied with for the following reasons :

4. Consequently, this opinion has been established in respect of the following parts of the international application :

   [X] all parts

   [ ] the parts relating to claim Nos.

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims 9-27	YES
	Claims 1-8 and 28-30	NO
Inventive step (IS)	Claims 9-27	YES
	Claims 1-8 and 28-30	NO
Industrial applicability (IA)	Claims 1-30	YES
	Claims	NO

2. Citations and explanations :

D1. WO 03/066086 DEVELOGEN AKTIENGESELLSCHAFT FUR ENTWICK-LUNGBIOLOGISCHE FORCHUNG, 14 August 2003.

D2. MORRISETT, J.D. et al. Journal of Lipid Research (2002) *Effects of sirolimus on plasma lipids, lipoprotein levels, and fatty acid metabolism in renal transplant patients*. Vol.43, pp1170-1180.

D3. FISHER, W.R. et al. . Journal of Lipid Research (1998) *Apolipoprotein B metabolism in hypertriglycerimedic diabetic patients administered either a fish oil- or vegetable oil-enriched diet*. Vol.39, pp.388-401.

D4. FISHER, E.A. et al. :Journal of Biological Chemistry (2001) *The Triple Treat to Nascent Apolipoprotein B*. Vol.276, No.30, pp.27855-27863.

D1 discloses nucleic acid sequences encoding casein kinase 1 (CK1), GABA receptor associated protein (GABARAP), cdc10 and the polypeptides encoded thereby and the use of these sequences or effectors thereof in the diagnosis, study, prevention, and treatment of diseases and disorders related to body-weight regulation, for example, metabolic diseases such as obesity as well as related disorders such as hypertension, coronary heart disease, hypercholesterolemia, and dyslipidemia.

D2 discloses the effects of sirolimus (rapamycin) on plasma lipids and fatty acid metabolism in renal transplant patients. Treatment with rapamycin induced an increase in total plasma cholesterol level, LDL-cholesterol levels and mean triglyceride levels.

D3 discloses that fish oil diet (rich in Ω-3 fatty acids eicosapentaenoic acid (EPA)) decreased triglycerides and very-low-density-lipoprotein (VLDL)-apoB levels in hypertriglyceridemic, non-insulin-dependent diabetic subjects.

D4 discloses that nascent apoB is subject to endoplasmic reticulum (ER)-associated degradation, re-uptake, and a third distinct degradative pathway that appears to target lipoproteins after considerable assembly and involves a post-ER compartment and PI3K signalling. In particular, cell fractionation showed that Ω-3 fatty acids induced a loss of apoB100 from the Golgi, while sparing apoB100 in the ER, indicating post-ER process. To determine the signalling involved, they used wortmannin, a PIB kinase inhibitor, which blocked most, if not all, of the Ω-3 fatty acid effect.

Novelty and Inventive step:
The subject-matter of claims 1-8 and 28-30 lacks novelty under Article 33(2) PCT as being anticipated by each of D1-D3.

The technical problem to be solved by the present invention is to provide a method of identifying "autophagocytosis modulating compounds" and to modulate serum levels of triglycerides and/or VLDL in a patient, using said compounds.

The prior art documents D1-D3 disclose the use of GABARAP (D1), rapamycin (D2) and EPA (D3) to modulate triglyceride levels in a patients. The "autophagocytosis inducing/inhibiting compounds" of the present application are defined as to include GABARAP, rapamycin and EPA.

The method of claims 9-27, for identifying "autophagocytosis inducing/modulating compounds" in a cell culture system, appears to be new under Article 33(2) PCT.

Continued in Supplemental Box.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claims 1, 3, 5, 7, 9, 16, 28 and 30 lack clarity under Article 6 PCT. The expressions "autophagocytosis inducing compound" and "autophagocytosis modulating compound" are vague and do not serve to distinctly and explicitly define the compounds contemplated by the Applicant.

Claims 1, 3, 5, 7, 9, 16, 28 and 30 are not fully supported by the description under Article 6 PCT. The "autophagocytosis inducing/modulating compound" contemplated in the present application includes, among others, MapILC3, GABARAP, GATE16, Class III PI3 kinase, wortmannin and rapamycin. However, no support can be found in the present application for any "autophagocytosis inducing/modulating compound" other than EPA. In addition, claims 28 and 29 are directed toward hoped-for-products and are thus broad enough to encompass any "autophagocytosis inducing/modulating compound", including yet-to-be-discovered proteins, molecules and compounds which have neither been disclosed nor contemplated by the Applicant.

Claims 1, 3, 28 and 30 are not fully supported by the description under Article 6 PCT. No support can be found in the present application that the use of an "autophagocytosis inducing/modulating compound" results in the reduction or modulation of triglycerides and/or VLDL and/or cholesterol serum levels in a patient.

Claims 2, 4 and 6 are not fully supported by the description under Article 6 PCT. No support can be found in the present application for the use of MapILC3, GABARAP, GATE16 or class III PI3 kinase in reducing serum levels of triglycerides and/or VLDL and/or cholesterol, for preparing a medicament useful for reducing serum levels of triglycerides and/or cholesterol or for the treatment or prevention of hypertriglycerimedia, hyperlipidemia, hypercholesterolemia, hyperproteinemia, atherosclerosis, arteriosclerosis, peripheral artery disease, coronary artery disease, congestive hear failure, myocardial ischemia, myocardial infarction, ischemic stroke, hemmorrhagic stroke, restenosis, diabetes, insulin resistance, metabolic syndrome, renal disease, hemodialysis, glycogen storage disease type I, polycystic ovary syndrome, secondary hypertriglyceremia or combinations thereof.

Claims 5, 7 and 30 are not fully supported by the description under Article 6 PCT. No support can be found in the present application for the use of an "autophagocytosis inducing compound" or "autophagocytosis modulating compound" for the treatment or prevention of hypertriglycerimedia, hyperlipidemia, hypercholesterolemia, hyperproteinemia, atherosclerosis, arteriosclerosis, peripheral artery disease, coronary artery disease, congestive hear failure, myocardial ischemia, myocardial infarction, ischemic stroke, hemmorrhagic stroke, restenosis, diabetes, insulin resistance, metabolic syndrome, renal disease, hemodialysis, glycogen storage disease type I, polycystic ovary syndrome, secondary hypertriglyceremia or combination thereof.

Claims 9 and 16 lack clarity under Article 6 PCT. The expression "autophagocytosis marker" is vague and does not serve to distinctly and explicitly define the markers contemplated by the Applicant

Claim 25 lacks clarity under Article 6 PCT. Claim 25 is directed toward a method of treating or preventing a disorder comprising administering a therapeutically effective amount of the pharmaceutical composition according to claim 25. However, claim 25 is not directed to a composition but a method.

Claims 1, 3, 5, 7, 9, 16, 28 and 30 do not comply with Rule 6.3 (a) of the Regulations under the PCT. The description discloses a method of identifying "autophagocytosis modulating compounds" and to modulate serum levels of triglycerides and/or VLDL in a patient, using said compounds. However, claims 1, 3, 5, 7, 9, 16, 28 and 30 do not contain any technical features that would define the matter for which protection is sought.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box No. V

In view of each of D1-D3, claims 1-8 and 28-30 also lack an inventive step under Article 33(3) PCT.

Further, D4 discloses that that nascent apoB is subject to ER-associated degradation, re-uptake, and a third distinct degradative pathway that appears to target lipoproteins after considerable assembly and involves a post-ER compartment and PI3 kinase signalling. In particular, cell fractionation showed that Ω-3 fatty acids induced a loss of apoB100 from the Golgi, while sparing apoB100 in the ER, indicating post-ER processing. To determine the signalling involved, D4 used wortmannin, a PI3 kinase inhibitor, which blocked most, if not all, of the Ω-3 fatty acid effect. One skilled in the art would use the teachings of D4, the use of Ω-3 fatty acids (including EPA) or wortmannin, in combination with the teachings of any of D1-D3 to modulate apoB levels, and ultimately, triglyceride and/or VLDL and/or cholesterol levels in a patient in need thereof. Therefore, in view of D4 and D1-D3, claims claims 1-8 and 28-30 lack an inventive step under Article 33(3) PCT.

Industrial applicability:

For the assessment of the present claims on the question of industrial applicability, no unified criteria exist in the PCT Contracting States. Further, the patentability of said claims can depend upon their formulation. Accordingly, although the methods *per se* defined claims 1, 2, 5, 6 and 30 relate to subject-matter which the Authority is not required to examine under Rule 67.1(iv) of the PCT, the use of the compounds referred therein for medical purpose appears to represent subject-matter that has industrial applicability under PCT Article 33(4). Therefore, claims 1-30 have industrial applicability under PCT Article 33(4).